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Metastatic breast cancer subtypes and central nervous system metastases

C. Aversa, V. Rossi, E. Geuna, R. Martinello, A. Milani, S. Redana, G. Valabrega, M. Aglietta, F. Montemurro

Abstract

Background: Breast cancer (BC) subtypes have different survival and response to therapy. We studied predictors of central nervous system metastases (CNS-M) and outcome after CNS-M diagnosis according to tumor subtype.

Patients and methods: 488 patients with diagnosis of metastatic BC were retrospectively evaluated. According to the combination of hormone receptors (HR) and HER2 status, tumors were grouped in: Luminal (Lum), Luminal/HER2+, pure HER2-positive (pHER2+) and triple negative (TN). Time to CNS progression, CNS-M free interval and Overall Survival (OS) after CNS-M occurrence were compared by the log-rank test. Cox-proportional hazard models were used to study predictor factors associated with CNS progression, including tumor subtype and all potentially clinical relevant variables.

Results: 115 patients (pts) developed CNS-M with a median time to CNS progression of 31 months. The rate of CNS-M by subtype was: Lum 14%, Lum/HER2+ 35%, pHER2+ 49%, TN 22% ($p < 0.001$). Compared with Lum tumors, Lum/HER2+ (HR 2.514, $p < 0.001$), pHER2+ (HR 6.799, $p < 0.0001$) and TN (HR = 3.179, $p < 0.001$) subtypes were at higher risk of CNS-M. Median OS in months after CNS-M was: Lum 7.4, Lum/HER2+ 19.2, pHER2+ 7, TN 4.9 ($p < 0.002$). Belonging to the Lum/HER2+ subtype (HR 0.48, $p < 0.037$) and having isolated CNS (HR 0.37, $p < 0.004$) predicted significantly reduced risk of death.

Conclusions: After CNS-M, the Lum/HER2+ subtype appears associated with the longest OS. Prospective clinical trials would be required for evaluating the potential role of screening for asymptomatic CNS lesions and of more aggressive CNS-M treatment in Lum/HER2+ subtype.

Keywords: Breast neoplasms; BC subtypes; Brain metastases; Survival outcome.

Introduction

The incidence of symptomatic central nervous system metastases (CNS-M) in women with breast cancer (BC) was reported in the range of 10%-16% in historical series [1] and [2]. While these figures referred to CNS-M presenting clinically during the course of metastatic disease, the real incidence of this metastatic localization has been known to be higher. In fact, on account of autopsy series, rates as high as 30% in patients dying from BC without clinically overt CNS-M have been reported [1] and [3]. Indeed, CNS-M generally occur as a late event in the natural history of metastatic BC. For this reason, and since the improvement in systemic treatments contrasts with the relative lack of efficacy of antitumor agents in the CNS, the incidence of clinically overt CNS-M seems to have raised significantly in the last two decades [4]. As a consequence, the optimal management of patients at risk of, or with diagnosed CNS-M is an unmet medical need and a major focus for research [4]. The prognosis of patients with CNS-M is, in fact poor, with survival rates of only 20% at one year from first diagnosis and less than 2% at two years [5]. Furthermore, CNS involvement is often associated with neurological complications that have a major impact on patients' quality of life. [4] There is increasing recognition that breast cancer is a collection of heterogeneous diseases. A seminal paper by Perou and colleagues has revealed that at least 4 major breast cancer subtypes can be identified based on distinct gene expression patterns [6]. Although more recent work in the field has added complexity to this classification [7], it is clear that tumor subtype influences all aspects of the natural history, pattern of relapse and response to treatments of breast cancer [8]. Indeed, single

biological factors as estrogen receptor (ER) and/or progesterone receptor (PgR) status and human epidermal growth factor receptor 2 (HER2) overexpression have proven to be associated the risk of developing CNS-M in the past [9], [10] and [11]. These immunohistochemical (IHC) markers may be combined to achieve a reasonable approximation of the molecularly defined subtypes [12]. Consequently, several authors have recently analyzed the impact of breast cancer subtype defined by ICH on incidence of CNS-M and subsequent survival [13], [14], [15], [16] and [17]. Overall, these analyses identify the triple-negative (ER and PgR and HER2 negative) and the HER2-positive subsets as those at the highest risk of CNS-M. However, while overall survival is shortest for triple-negative breast cancer, it results particularly long, usually in the range of 15-17 months, in HER2-positive patients, especially when systemic treatment is feasible after the diagnosis of CNS-M [13], [14], [15], [16], [17], [18], [19], [20] and [21]. Differently from what thought in the relatively recent past, heterogeneity of HER2-positive tumors according to HR expression has now been fully recognized [22], [23] and [24]. Both the HER2 and the HR pathway concur to the peculiar biology of this distinct entity and to its clinical behavior in adjuvant and metastatic setting. With these premises we set out to analyze predictors of CNS-M and the outcome after CNS recurrence according to tumor IHC-defined subtypes, with a focus on possible differences in the HER2-positive subset according to hormone receptor status.

Material and methods

Clinical records of 488 patients starting first-line chemotherapy for metastatic disease between June 1999 and March 2012 were identified from the medical charts of our Outpatient Clinic. All patients with HER2-positive disease received anti-HER2 treatment in addition to chemotherapy for metastatic disease. Median follow-up was 34 months (2-210 months). For each patient we collected the following data: date of first breast cancer diagnosis, stage at first diagnosis, ER and/or PgR expression, HER2 status, neoadjuvant/adjuvant chemotherapy and/or hormone therapy, exposure to anthracycline or taxanes as adjuvant treatment, exposure to endocrine therapy as adjuvant treatment and/or for metastatic disease, date and site of first metastatic recurrence, first chemotherapy or trastuzumab based treatment for HER2-positive disease, date of further metastatic recurrences, date of the first CNS-M diagnosis, treatments for CNS-M, status at last follow-up date or date of death. According to the combination of HR and HER2 status, tumors were grouped as follows: Luminal (Lum): HR+ (i.e. ER+ and/or PgR+)/HER2-, Luminal/HER2+ (Lum/HER2+): HR+/HER2+, pure HER2-positive (pHER2+): HR-/HER2+, and triple negative (TN): HR-/HER2-.

ER and PgR status was determined by immunohistochemical (IHC) analysis, with 1% cut off for positive result according to current guidelines [25]. The HER2 status determined by immunohistochemical (IHC) staining by the Dako HercepTest, with a 3+ score identifying positive cases. Uncertain results (2+ at IHC) were further analyzed with fluorescent in situ hybridization (FISH). A HER2/Cep17 ratio ≥ 2 was chosen to define HER2 amplification.

Statistical analyses

Comparisons between categorical variables were accomplished by the Fisher's or the Chi-square test, as appropriate. The following end points were evaluated by Kaplan Meier analysis: overall survival (OS), which was calculated from the date of first metastatic diagnosis to the date of death or last follow-up for alive patients; time to CNS progression, which was calculated from the date of the first diagnosis of metastatic breast cancer to that of the first documented CNS-M or last follow-up in patients without CNS-M; CNS-M free interval, which was calculated from the date of the first diagnosis of metastatic breast cancer to that of the first documented CNS-M restricted to patients who developed the event: OS after CNS-M, which was

calculated from the date of the first CNS-M diagnosis to date of death or last follow-up for alive patients. Kaplan Meier curves were compared by the log-rank test. Factors associated with CNS progression and OS after CNS-M were evaluated by Cox hazard analysis where the effect of tumor subtype was analyzed together with that of other potentially relevant clinical variables. These included: age at diagnosis of metastatic breast cancer, stage at first diagnosis, disease free survival (from first localized disease to metastatic progression), exposure to adjuvant chemotherapy and to neoadjuvant or adjuvant regimens containing anthracyclines and/or taxanes, pattern and number of metastatic sites, and type of first-line chemotherapy or trastuzumab containing treatment. Because of the relatively small number involved and the exploratory nature of this analysis, we did not test for multiple comparisons. Statistical analyses were performed using the SPSS software 17.0. For all analysis statistical significance was set at $p < 0.05$.

Results

Patients and overall survival from the first diagnosis of metastatic disease

A total of 488 metastatic BC patients receiving chemotherapy between June 1999 and March 2012 were analyzed and [Table 1](#) summarizes their relevant demographic characteristics. Median age at first breast cancer diagnosis was 51 years and median age at first metastatic recurrence was 55 years. A total of 267 (55%), 75 (15%), 79 (16%) and 64 (13%) patients had Lum, Lum/HER2+, pHER2+ and TN cancers, respectively. In 3 (1%) patients the tumor subtype could not be determined. A total of 249 (51%) patients had received adjuvant chemotherapy and 274 (56%) had received adjuvant hormonal therapy. Of the 154 patients with HER2-positive disease, a total of 15 (10%) who underwent breast cancer surgery after September 2005 (when adjuvant trastuzumab was registered for adjuvant use in Italy), received adjuvant trastuzumab added to chemotherapy.

Table 1: Main characteristics of patients study group.

Variable	N	%
Total	(n = 488)	
Median age at first BC diagnosis (years range)	51 (22–83)	
Median age at first metastatic recurrence (years range)	55 (24–85)	
Stage at first metastatic BC diagnosis		
I/II	222	46
III	138	28
IV	104	21
Unknown stage	24	5
Hormone receptor status		
ER + e PgR+	235	48
ER + e PgR–	88	18
ER– e PgR+	8	2
ER– e PgR–	143	29
Unknown	14	3
HER2 status		
Positive	154	32
Negative	334	68
Biological subgroup		
Lum	267	55
Lum/HER2+	75	15
pHER2	79	16
TN	64	13
Unknown	3	1
Adjuvant chemotherapy	249	51

Variable	N	%
Adjuvant hormonotherapy	274	56
Median disease-free survival (months range)	28 (0–311)	
First metastatic sites		
Liver	243	50
Lung	155	32
Bone	312	64
Soft tissue/lymphnodes	293	60
Effusion	65	13
Brain	23	5
Visceral involvement at first diagnosis of metastases	327	67
Number of metastatic sites at first diagnosis of metastases		
One	141	29
Two	127	26
Three or more	220	45
Median time to the first BC metastasis from the diagnosis of EBC (months, range)	28 (0–306)	
Median time to CNS from the diagnosis of EBC (months, range)	64 (3–350)	
Median time to CNS progression from the first diagnosis of BC metastasis (months, range)	31 (0–192)	
Lum/HER2+	96 (64–129)	
pHER2+	32 (0–74)	

BC = breast cancer ER = estrogen receptor PgR = progesterone receptor EBC = early breast cancer.

Table 2 summarizes the types of first-line chemotherapy received by patients. All patients with HER2-positive metastatic BC received trastuzumab-based treatment, with most of them receiving continuous trastuzumab beyond disease progression, in combination with alternative chemotherapy agents or hormonal therapy. At the time of the analysis, 343 patients had died because of disease progression. The median OS from first metastatic progression was 40.5 months (95% C.I. 37.2–43.8). [Fig. 1](#) shows the Kaplan Meier curves of OS according to subtype. Median OS for patients with Lum, Lum/HER2+, p-HER2+ and TN tumors was 44.4 months (95% 37.7–51.2), 55.3 months (95% C.I. 37.4–73.3), 35.9 months (95% C.I. 29.7–42.1) and 27.1 months IC (95% C.I. 22.6–31.6), respectively (overall log-rank test, $p = 0.0001$).

Table 2: First line chemotherapy treatment.

Treatment	N	%
Containing taxanes (no anthracyclines)	267	55
Containing anthracyclines (with or without taxanes)	14	3
Containing vinorelbine	95	20
Capecitabine	42	9
Other treatments ^a	35	7

^a In 30 patients with Lum/HER2+ tumors the hormonal therapy was the first treatment. In 5 patients details of the first line of therapy were unknown.

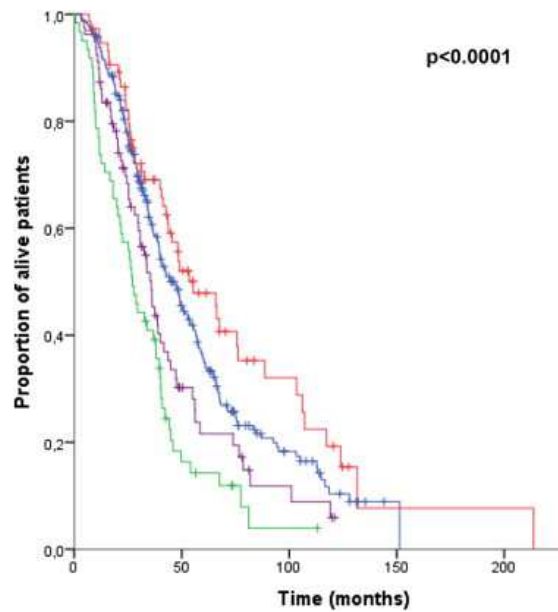


Fig. 1. Kaplan Meier curve estimates of overall survival probability according to biological subgroup. Red, Lum/HER2+; blue, Lum; purple, pHER2+; green, TN

CNS progression and subsequent outcome

At the time of the analysis 115 patients (24%) had developed CNS-M. In all cases CNS-M were diagnosed following CNS imaging performed because of neurological symptoms. The proportion of CNS-M in each tumor subtype was: 14%, 35%, 49%, and 22% in Lum, Lum/HER2+, pHER2+ and TN tumors, respectively (Table 3, $p < 0.001$). Isolated CNS-M (no concomitant disease progression in sites outside the CNS) occurred in 30 pts (26%). This pattern of relapse was observed more frequently in patients with HER2-positive tumors [13 pts (43%) in Lum/HER2+ and 13 pts (43%) in pHER2+] compared to the other subgroups [2 pts (7%) in Lum and 2 pts (7%) in TN, $p < 0.0001$]. Most of the patients with isolated CNS-M received whole brain radiotherapy (17 pts). Of the remaining 13 patients with isolated CNS-M, 7 were managed with surgery plus radiotherapy and 6 with stereotactic radiotherapy. Most of the patients with CNS-M associated with extracranial progression received whole brain palliative radiation therapy with or without anticancer therapy (41 patients). A small group received surgery plus radiotherapy (3 pts) or stereotactic radiotherapy (11 pts) and the remaining 30 patients, who had extensive extra-CNS progression, received systemic chemotherapy alone (11 pts) or best supportive care (19 pts). In patients stratified according to tumor subgroup, the median time to CNS progression was not reached for Lum and TN tumors, and was 96 months (95% C.I. 63.9–128.6) and 32 months (95% C.I. 0–73.5) for Lum/HER2+ and pHER2+ tumors, respectively (Fig. 2, overall log-rank test, $p < 0.0001$). The overall median CNS-M free interval, restricted to patients who developed CNS-M, was 17.6 months (95% C.I. 14.1–21.3). According to subtypes, CNS-M free interval was 17 months (95% C.I. 8.7–25.3), 24.6 months (95% C.I. 14.6–34.6), 16.4 months (95% C.I. 11.8–21), and 9.2 months (95% C.I. 8.4–10.1) for Lum, Lum/HER2+, pHER2+ and TN tumors, respectively (Fig. 3, overall log-rank test, $p < 0.014$). A multivariate analysis conducted in the whole dataset confirmed that, compared with Lum tumors, Lum/HER2+ (HR 2.514, $p < 0.001$), pHER2+ (HR 6.799, $p < 0.0001$) and TN (HR = 3.179, $p < 0.001$) subtypes were at higher risk of CNS-M. Having more than three metastatic sites (HR = 2.712, $p < 0.0001$) and stage III as initial breast cancer presentation (HR = 4.836 $p < 0.0001$) resulted also independently associated with higher risk of CNS-M. By contrast older age (HR = 0.943, $p < 0.0001$) was associated with low risk of CNS-M development; for every additional year of age of first diagnosis of metastatic breast cancer was observed a reduction in the risk of brain metastases of approximately 6%.

Table 3: Brain metastases progression according to biological subgroup.

Biological subgroup	Patients with brain metastases	Patients without brain metastases	<i>p</i>
Lum	36 (14)	231 (86)	<0.001
Lum/HER2+	26 (35)	49 (65)	
pHER2	39 (49)	40 (51)s	
TN	14 (22)	50 (78)	

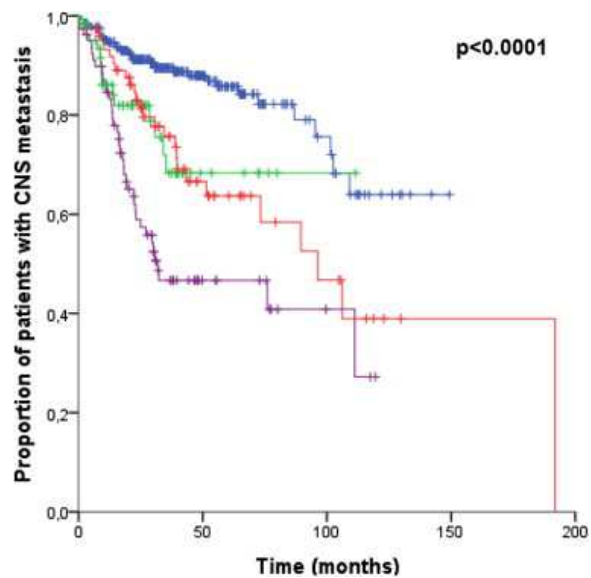


Fig. 2. Kaplan Meier curve estimates of median time to CNS progression from the first metastatic diagnosis in overall population. Red, Lum/HER2+; blue, Lum; purple, pHER2+; green, TN

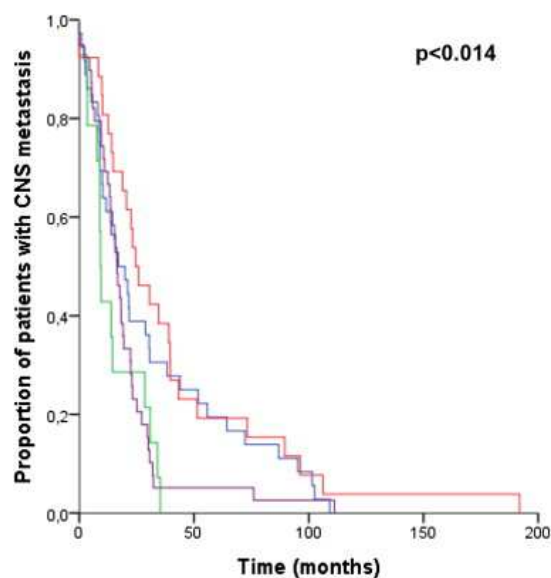


Fig. 3: Kaplan Meier curve estimates of median CNS-M free interval from the first metastatic diagnosis in patients developing CNS-M. Red, Lum/HER2+; blue, Lum; purple, pHER2+; green, TN

Survival after CNS progression

Ninety of the 115 patients developing CNS-M had died at the time of this analysis. The median overall OS after CNS-M was 8.8 months (95% C.I. 6.1–11.5). [Fig. 4](#) shows OS after CNS-M according to subtype. We observed a median OS after CNS-M of 7.4 months (95% C.I. 4.4–10.4), 19.2 months (95% 1.9–36.5), 7 months (95% C.I. 3.4–10.8), and 4.9 months (95% C.I. 0.0–11.1) for Lum, Lum/HER2+, pHER2+ and TN tumors, respectively ($p < 0.002$).

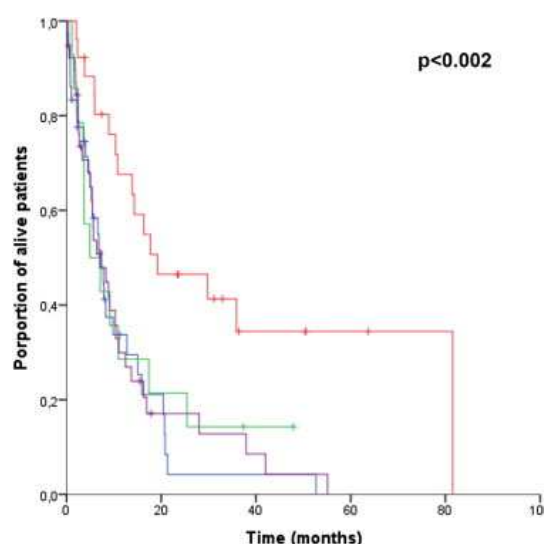


Fig. 4: Kaplan Meier curve estimates of overall survival after CNS-M diagnosis according to biological subgroup. Red, Lum/HER2+; blue, Lum; purple, pHER2+; green, TN.

Multivariate analysis ([Table 4](#)) revealed that belonging to the Lum/HER2+ subtype (HR 0.48 compared with the Lum subtype, $p < 0.037$) and having isolated CNS (HR 0.37, compared with CNS-M plus systemic progression, $p < 0.004$) predicted significantly reduced risk of death in patients with CNS-M.

Table 4: Multivariate analysis of factors associated to survival after CNS progression.

Variable	HR	IC 95%	<i>P</i>
Biological subgroup			
Lum	1		
Lum/HER2+	0.481	0.242–0.956	0.037
pHER2	1.093	0.634–1.884	0.749
TN	0.741	0.372–1.480	0.396
Isolated CNS progression	0.374	0.192–0.730	0.004
DFS (months)	0.997	0.989–1.004	0.358

DFS = disease free survival.

Discussion

Central nervous system involvement is an emerging medical priority in patients with breast cancer. In fact, in recent years, its incidence is rising, and this may be due to prolonged survival achieved by the expanding armamentarium of active treatments to control extracerebral disease. Indeed, in this large dataset of 488 metastatic breast cancer patients, we observed that about one quarter of them developed CNS-M, a figure that is higher than previous historical reports [1] and [2]. Furthermore, we registered a median time to CNS-M progression of 31 months which confirms that, overall, CNS-M could be considered as a late event in the natural history of treated metastatic breast cancer. Interestingly, we found that women with Lum/HER2+ tumors developed CNS-M with a median time to the event of 96 months from the date of early breast cancer diagnosis, which exceeds the 55 months median OS reported for this subgroup. Intuitively, the longer the time during which occult CNS metastases could outgrow, the higher the incidence of this type of metastases. In addition, we also confirmed that women with HER2-positive metastatic disease, who received trastuzumab-based chemotherapy, are at the highest risk of CNS-M, but stratification according to hormone receptor status revealed interesting differences. Patients with Lum/HER2+ tumors had a trend to develop CNS-M slightly less frequently and at later times compared with those with pHER2+ tumors (median time to CNS progression 96 vs 32 months). Moreover, Lum/HER2+ tumors stood out as the best prognostic group also considering CNS-M free interval. Indeed, compared with other tumor subtypes, patients with Lum/HER2+ tumors had the highest median CNS-M free interval (24.6 months), probably due to the addition of hormonal therapy to the anti-HER2 agents in metastatic setting. At multivariate analysis, tumor subtype retained its independent prognostic value with respect to CNS-M, together with younger age at diagnosis of metastatic disease, stage III disease at first diagnosis of breast cancer, and more extensive metastatic disease ($p < 0.001$). The hazard ratio was confirmed highest for pHER2+ tumors. Before discussing the potential implications of our analysis, we have to acknowledge its main limitations. We selected patients admitted to our outpatient clinic to receive chemotherapy for metastatic disease and a number of them had their surgery for primary breast cancer outside our Institution. Because of missing or unreliable information on Ki67, our stratification into immunohistochemical subtypes does not match with what recommended by current guidelines [12], in particular for the ability to distinguish between luminal A and B/HER2-negative subtypes [26]. Furthermore, patients with Lum tumors in this series developed endocrine resistance at some point of their clinical course and were prescribed chemotherapy. We may therefore speculate that the Lum group was enriched in aggressive tumors, regardless of their initial subtype. This calls into the question another potential caveat, which is represented by change in the HR and HER2 expression during the course of metastatic progression and through different lines of treatments for metastatic disease. For the majority of patients, subtyping was based on determinations performed on the primary, rather than the metastatic tumor. A change in hormone-receptor expression has been seen to occur at a clinically significant rate [27]. Similar changes in hormone receptor status have been also recently described in papers comparing CNS-M with primary tumors, whereas HER2 status tends to remain stable [28] and [29]. However, the differences in proportion and time to development of CNS-M that we found confirm that we analyzed different clinical and biological entities. This factor becomes particularly relevant considering our main finding that the Lum/HER2+ subset showed the best prognosis after the diagnosis of CNS-M. In fact, a number of recent reports suggest that, with the availability of anti-HER2 treatments, the survival of patients with HER2-positive tumors diagnosed with CNS-M and who are still amenable to medical treatment is favorable, compared with other subgroups [13], [14], [15], [16], [17], [18],[19], [20] and [21]. Here we found that this effect is limited to HER2-positive tumors that co-expressed hormone receptors (Lum/HER2+). Interestingly, pHER2+ tumors had a median OS after CNS-M similar to Lum and just slightly longer than TN tumors. Because of the

growing body of data suggesting a different biology of HER2-positive disease according to HR status [24], we believe that the lower incidence, longer time to develop CNS-M and longer OS after CNS-M in patients with Lum/HER2+ tumors are unlikely to be a random finding. Recently, a few retrospective studies in breast cancer patients with CNS-M evaluated the incidence and clinical outcomes of CNS-M according to breast cancer subtypes reporting separately HER2-positive tumors according to HR coexpression [13], [15], [30] and [31]. While in the paper by Sperduto and colleagues the OS after CNS-M was similar in HER2-positive patients stratified according to hormone receptor status, Laurent-Braccini and colleagues found a trend similar to ours. The median OS after CNS-M was 14.9 months and 8.9 months for Lum/HER2+ and pHER2 tumors, respectively, although this difference was not statistically significant. In their analysis of 119 patients with breast cancer and CNS-M, Anders and colleagues found that the median OS after CNS-M was longest (1.27 years) in Lum/HER2+ tumors compared with other subtypes [13]. Finally, Berghoff and colleagues, who analyzed 213 women with breast cancer and CNS-M, found that the median brain metastasis-free interval (time from the diagnosis of extracranial metastases to that of CNS-M) was significantly longer according to HR status in HER2+ tumors (26 vs 15 months for HR+ and HR- tumors, respectively, $p = 0.033$) [15], another finding consistent with our results. Unfortunately, all these reports have methodological weaknesses. Definitions of hormone receptor positivity (cutoffs, or whether the primary tumor or the CNS-M, were tested) are not often detailed and centralized revision of hormone receptor status and HER2 was not performed in the majority of them, including our own. With these limitations in mind, however, we believe that evidence consistently points at a difference in the CNS-M behavior of HER2-positive tumors according to HR status. A deeper comprehension of the molecular basis of these findings could be provided by gene expression profile analysis. Metastatic colonization of different target organs seems to be a genetically defined, highly selective process that relies on specific properties of cancer cells and their interactions with organ microenvironment [32]. For example, Massagué and colleagues were able to identify a gene expression signature associated with breast cancer brain metastasis (BrMS). Among the 17 genes whose expression distinguished primary tumors with different probability of developing brain metastasis, 6 were shared with a 18-gene signature of lung metastasis. Intriguingly, some of these shared genes encoded for proteins involved in invasion and extravasation (MM1), disruption of endothelial junctions (ANGPTL4) and cancer cell migration (FSCN1). More importantly, by using an experimental model mimicking the blood-brain barrier, the authors found that the expression of COX2 and the genes for two EGFR ligands (HBEGF and EREG), could specifically prime breast cancer cells for extravasation into the brain [33]. We therefore believe that our findings may have two potential implications in the way we currently conceive the event of CNS-progression in breast cancer patients: first, for the majority of patients and regardless of their main immunohistochemical features (Lum, pHER2+ and TN), little progress has been made over recent years in extending survival after CNS-M, which averages 7–8 months. In fact, CNS progression remains the main cause of death in women with metastatic breast cancer and CNS-M [34]. Second, the prolonged OS found in Lum/HER2+ patients would make CNS-M screening in asymptomatic patients an attractive option to detect early events that could be amenable to local therapies. By virtue of a biology where the effect of HER2 on aggressiveness is somewhat mitigated by concomitant HR expression, and with endocrine therapy being an additional option in the therapeutic armamentarium, these patients may experience unexpectedly long OS if correctly managed. It is also important to keep in mind that the findings presented in our series are likely to be just the tip of the iceberg of a potentially larger number of factors that may play an important role in promoting organ-specific metastasis. Elucidating these mechanisms would likely result in improvement in the outlook of breast cancer patients either at risk of developing or with established CNS metastases.

Conflict of interest statement

Filippo Montemurro has served as member of Speaker's Bureau for Astra Zeneca and for Hoffmann La Roche SPA. All the other authors have no conflict of interest to declare.

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